The Toxicity, Pathophysiology, and Treatment of Acute Hydrazine Propellant Exposure: A Systematic Review

Capt HoanVu N. Nguyen, MC USAF[*]*; James A. Chenoweth MD MAS*[†]*;*
Col Vikhyat S. Bebarta MC USAF[‡,§]*; BG Timothy E. Albertson USA (Ret.)*[‖]*;*
Capt Craig D. Nowadly, MC USAF[¶]

ABSTRACT

Introduction:
Hydrazines are highly toxic inorganic liquids that are used as propellants in military and aviation industries, such as the U.S. Air Force F-16 Emergency Power Unit and SpaceX SuperDraco Rockets. The most commonly used derivatives include hydrazine, monomethylhydrazine, and 1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine). Industrial workers in close contact with hydrazines during routine maintenance tasks can be exposed to levels well above the National Institute for Occupational Safety and Health relative exposure limits.

Materials and Methods:
A systematic review was performed using PubMed, Web of Science, Google Scholar, National Aeronautics and Space Administration Technical Server, and Defense Technical Information Center, and data related to hydrazine exposures were searched from inception to April 2020. Publications or reports addressing hydrazine toxicity, pathophysiology, and treatment of hydrazine fuel exposure were selected.

Results:
Acute toxic exposures to hydrazine and its derivatives are rare. There are few case reports of acute toxic exposure in humans, and data are largely based on animal studies. The initial search identified 741 articles, manuscripts, and government reports. After screening for eligibility, 51 were included in this review. Eight articles reported acute exposures to hydrazine propellant in humans, and an additional 14 articles reported relevant animal data.

Conclusions:
Exposure to small amounts of hydrazine and its derivatives can cause significant soft tissue injury, pulmonary injury, seizures, coma, and death. Neurologic presentations can vary based on exposure compound and dose. Decontamination is critical as treatment is mainly supportive. High-dose intravenous pyridoxine has been suggested as treatment for hydrazine-related neurologic toxicity, but this recommendation is based on limited human data. Despite recent research efforts to generate less toxic alternatives to hydrazine fuel, it will likely continue to have a role in military and aviation industries. Aerospace and military physicians should be aware of the toxicity associated with hydrazine exposure and be prepared to treat hydrazine toxicity in at-risk populations.

[*]Rocky Mountain Poison & Drug Safety, Denver Health and Hospital Authority, Denver, CO, 80204, USA

[†]Department of Emergency Medicine, University of California at Davis, Sacramento, CA, 95817, USA

[‡]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, 80045, USA

[§]CU Anschutz Center for COMBAT Research, University of Colorado School of Medicine, CO, 80045, USA

[‖]Department of Internal Medicine, University of California at Davis, Sacramento, CA, 95817, USA

[¶]Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, TX, 78234, USA

The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, University of Colorado, University of California at Davis, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, or the Department of Defense or the U.S. Government.

doi:10.1093/milmed/usaa429

INTRODUCTION

Hydrazine is an inorganic, colorless, highly toxic reducing agent that is used as a propellant in military and aerospace industries.[1] Hydrazine was first developed as a fuel by German scientists during World War II,[2] and interest in the use of hydrazine and its alkyl derivatives flourished during the postwar period.[3] Hydrazine saw widespread adoption as a reliable, powerful propellant with liquid properties similar to water.[4] Unlike conventional combustible fuels that require an ignition source, hydrazine can act as both a hypergolic propellant and a monopropellant.[5,6] Although these industrial advantages make it ideal for use in specific aviation and rocket applications, hydrazine poses a threat to human life and environmental safety. Hydrazine and its derivatives have neurotoxic properties and because of their reducing capabilities, even small amounts of hydrazine can cause soft tissue injury, pulmonary injury, seizures, coma, and death.[7]

The hazards of occupational exposures to jet aircraft fuels have been reported in the medical literature since the mid-1950s.[8] The wide application of hydrazine fuels and

resultant risk for potential exposure to personnel prompted extensive toxicology studies on hydrazine and its methylated derivatives from the late 1950s through the mid-1980s. These studies serve as the basis for most care and treatment recommendations for toxic exposures to these compounds.

Today, over 45,000 metric tons of hydrazines are produced annually worldwide, with hydrazine, monomethylhydrazine (MMH), and 1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine, UDMH) being the most commonly used propellant fuels.[9,10] It is known for its use in the General Dynamics F-16 Falcon and Lockheed U-2 Emergency Power Units (EPU), SpaceX SuperDraco rockets, and countless spacecraft orbital maneuvering thrusters.[11–14] Fortunately, because of the effective safety regulations of military and industrial agencies, there are few reported cases of acute hydrazine exposures in humans.[15,16] As a result, the evidence for the mechanisms of hydrazine toxicity and treatments are based largely on animal studies or isolated case reports. In this systematic review, the pertinent literature regarding the toxic effects of hydrazine-based propellants and the treatments options available to military and industrial medical providers will be analyzed. Emphasis will be placed on the acute occupational exposure to these compounds in the military and aerospace environment.

METHODS

A systematic review of the available literature was performed for articles and abstracts related to hydrazine exposures. All human and animal studies, case series, case reports, or reviews were considered for inclusion in this review. Data were abstracted systematically from a query of PubMed (National Center for Biotechnology Information, National Institutes of Health; Bethesda, MD, USA); Web of Science (Thomson Reuters; New York, NY, USA); Google Scholar (Google Inc.; Mountain View, CA, USA); National Aeronautics and Space Administration (NASA) Technical Server (NASA Langley Research Center; Hampton, VA, USA); and Defense Technical Information Center (Fort Belvoir, VA, USA) from inception to April 2020. A gray literature search was also performed using OpenGrey (INIST-CNRS—Institut de l'Information Scientifique et Technique; Paris, France) and Google. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.[17] Studies published in a language other than English without available translation and articles not specifically addressing acute hydrazine toxicity, pathophysiology, or treatment were excluded from this review.

The search strategy included free-text words (TW) and controlled vocabulary terms using medical subject headings (MeSH) for these topics, their synonyms, abbreviations, and alternate spellings. The primary search string included (hydrazine[TW]) AND (toxicology[MeSH] OR toxin[MeSH] OR occupational accidents[MeSH] OR accidents[MeSH] OR aviation[Mesh] OR safety[MeSH] OR spaceflight[MeSH]). References in each selected publication were also carefully screened for any additional relevant articles.

RESULTS

The initial search identified 721 articles, and an additional 20 articles were obtained through review of manuscript references. Records were screened manually by the authors for eligibility, and duplicates were removed based on the title and/or abstract contents. Of the remaining 79 publications, 28 addressed issues outside the scope of this systematic review. The remaining 51 articles were included in the review (Fig. 1). Eight articles reported acute exposures to hydrazine propellant in humans, which are summarized in Table I.[18–25] An additional 14 articles reported relevant animal data. The remaining articles were review papers, technical reports, or government documents.

DISCUSSION

The following discussion includes data from acute animal and human exposures to hydrazine and its derivatives. Long-term impacts of chronic, low-dose, industrial exposures to hydrazine (risk of malignancy, etc.) will not be discussed.

Chemical Structure and Exposure Data

Hydrazine (N_2H_2) is an oily liquid at room temperature, fumes in air, and has an ammonia-like odor. Fig. 2 displays the chemical structure of hydrazine and its relevant derivatives. Workers in close contact with hydrazine during routine maintenance tasks can be exposed to levels as high as 5 to 8 parts per million (ppm), well above the American National Institute for Occupational Safety and Health (NIOSH)-recommended ceiling relative exposure limit of 0.03 ppm (0.04 mg/m^3 2-hour time-weighted average).[26] The immediately dangerous to life or health concentration of hydrazine, based on animal research by Comstock et al. in 1954, is 50 ppm for a 30-minute exposure.[26,27] The alkyl hydrazines have similar physical characteristics, but may gradually discolor to yellow. The NIOSH relative exposure limit for MMH and UDMH are 0.04 ppm (0.08 mg/m^3) and 0.06 ppm (0.15 mg/m^3), respectively. The immediately dangerous to life or health concentrations for these compounds are 20 and 15 ppm, respectively, based on work by Jacobson et al. in the 1950s in rodents.[28] The odor threshold for most individuals is reported to be ~2 to 5 ppm, which is several orders of magnitude above the recommended exposure limit making human detection both unreliable and clinically concerning during acute and chronic exposures.[7,15] According to NASA, the 7-day Spacecraft Maximum Allowable Concentration for both hydrazine and MMH is 0.04 ppm.[29]

Toxicity and Pathophysiology

Skin Irritation and Soft Tissue Injury

Exposures to hydrazine on the skin can result in either contact dermatitis or caustic injuries with more significant exposures.

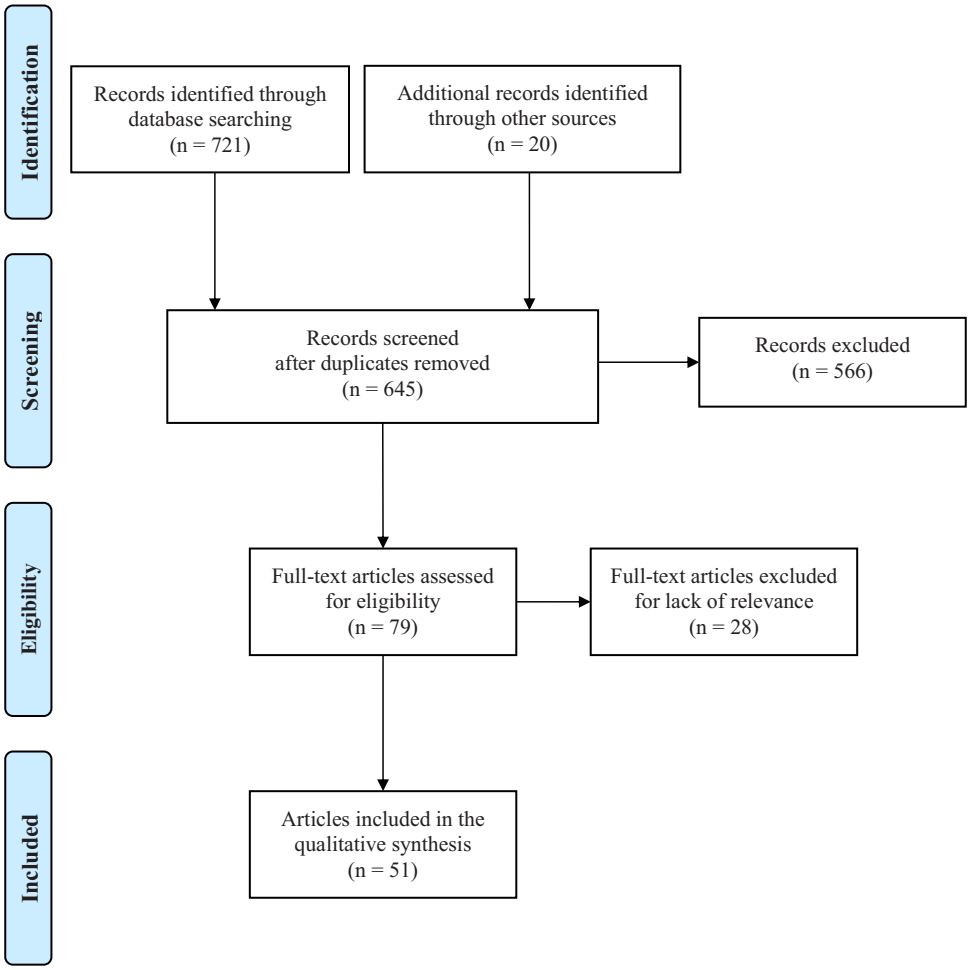

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of publications reporting on topics specific to hydrazine toxicity, pathophysiology, or treatment.

In animal studies where cutaneous absorption of hydrazine was tested, exposure on the skin resulted in a burned appearance and erythema within 2 minutes, which then progressed to papules and edema. This initial edema subsided, and then, the skin progressively darkened and progressed to a severe chemical burn.[30] Human cases of cutaneous exposure come primarily from the electroplating industry where hydrazine derivatives are used as a reducing agent in chemical solvents for electroplating. These exposures are generally mild and involve development of localized erythema consistent with contact or allergic dermatitis. Repeated exposures lead to development of eczema that resolves after exposure to hydrazine was removed.[31,32] Ocular exposures, typically from hydrazine vapors, are described to cause conjunctivitis, intense eye pain, miosis followed by mydriasis, corneal injury, and temporary blindness.[7,20] Pathophysiology of the cutaneous effects of hydrazine and its alkyl derivatives derive primarily from the caustic nature of hydrazine solutions. As a strong base, hydrazine and its derivatives can denature proteins and saponify adipose tissue, similar to other alkali-caustic burns.[7,33]

Pulmonary Injury

Inhalation exposures to hydrazine have been associated with pulmonary edema and effusions. Pulmonary edema with localized bronchial mucosal damage was observed in rats exposed to hydrazine.[27] Respiratory arrest in toxic exposures in animals were typically attributed to the neurotoxic and convulsive effects of the compounds rather than direct pulmonary injury.[27,34] Symptoms of dyspnea, sore throat, a burning sensation of nares and face, and chest tightness have been described after exposure to hydrazine/UDMH vapor. The exposed individuals were concluded to have developed pulmonary edema.[18] In a fatal case of inhalational and possibly cutaneous hydrazine toxicity, pleural effusions and pulmonary edema were noted.[20] It has been suggested that hydrazine causesmore direct pulmonary injury compared with either MMH or UDMH.[35] Pulmonary injury from hydrazine is likely similar to other irritant volatile compounds and related to its caustic nature.

TABLE I. Published Reports of Acute Hydrazine Propellant Toxicity in Humans

Author	Subject	Exposure	Notable symptoms	Notable interventions	Outcome
Frierson[18] (1965)	36-year-old male	Aerozine 50 vapor (50% hydrazine and 50% UDMH)	Headache, nausea, diaphoresis, sore throat, chest burning, twitching/clonic movements of the extremities, pulmonary edema	Pyridoxine 200 mg IV and 400 mg IM, dexamethasone 3 mg IV, supplemental oxygen, isoproterenol inhalation	Rapid improvement with full recovery, all labs normal over the next 3 weeks
	44-year-old male	Aerozine 50 vapor (50% hydrazine and 50% UDMH)	Severe dyspnea, hyperreactive reflexes, bilateral pulmonary edema	Pyridoxine 200 mg IV and 400 mg IM, dexamethasone 4 mg IV, supplemental oxygen, isoproterenol inhalation	Rapid improvement
Reid[19] (1965)	Young male	Accidental oral ingestion of "a mouthful to a cup" of liquid hydrazine	Emesis, progressive loss of consciousness, miosis with progressive mydriasis, intermittent agitation, seizures, ataxia, nystagmus, loss of vibration	Thiopentone-succinylcholine, mechanical ventilation, intravenous pyridoxine	Unknown
Sotaniemi et al.[20] (1971)	59-year-old male	Hydrazine (multiple acute doses over 6 months)	Conjunctivitis, tremor, jaundice, gastrointestinal bleeding, altered mental status, fever, hyperbilirubinemia, renal failure, atrial fibrillation, tracheitis/bronchitis, pneumonia	Thiethylperazine, phthalysulfathiazole, hemodialysis, intravenous B vitamins	Mental status improved but pneumonia worsened, leading to multisystem organ failure and death
Kirklin et al.[21] (1976)	36-year-old male	Hydrazine industrial explosion	22% Total body surface area (TBSA) burns, progressive loss of consciousness, miotic unresponsive pupils, persistent coma, hematuria, stridor, hepatic injury, hyperammonemia	Mechanical ventilation, pyridoxine 600 mg IM followed by 1 g infusion over 3 hours	Discharged hospital day 38, rapid neurologic recovery after pyridoxine
Harati and Niakan[22] (1986)	24-year-old male	Accidental oral ingestion of "a mouthful" of liquid hydrazine	Altered mental status, hepatic injury, peripheral neuropathy	Pyridoxine 10 g IV	Discharged, persistent neuropathy and lower extremity weakness for 6 months
Dhennin et al.[23] (1988)	31-year-old male	UDMH industrial explosion	53% Total body surface area (TBSA) burns, hypotension, reactive mydriasis and miosis, altered mental status, irregular theta and delta activity on EEG, gastrointestinal bleeding, hepatic injury	Pyridoxine 25 mg/kg, 25% IV, 75% IM × 4 doses; ornithine ketoglutarate 35 g/24 h, IV; phenobarbital 100 mg IM daily, mechanical ventilation	Discharged hospital day 68, persistent liver injury, polyneuritis
Kao et al.[24] (2007)	31-year-old male	Hydrazine fuel leak	Headache, dizziness, hepatic injury, lower extremity urticaria	None required	Full recovery, hepatic injury resolved by day 28
Binyamin et al.[25] (2018)	21-year-old male	Hydrazine vapor	Hepatic injury, rhabdomyolysis	Intravenous fluids	Discharged hospital day 2, hepatic injury resolved by day 21

Abbreviations: EEG, electroencephalogram; IM, intramuscularly; IV, intravenously; UDMH, unsymmetrical dimethylhydrazine.

Neurotoxicity

After exposure to hydrazine, MMH, and UDMH, neurologic effects vary from neurologic depression (coma) to neuroexcitation (seizures). The neurologic toxicity appears related to the specific compounds and exposure dose in both animal studies and human case reports. However, the data from human exposures are complicated by the fact that aerospace and military propellants often have mixtures of hydrazine compounds, creating the possibility of mixed toxic sequelae.

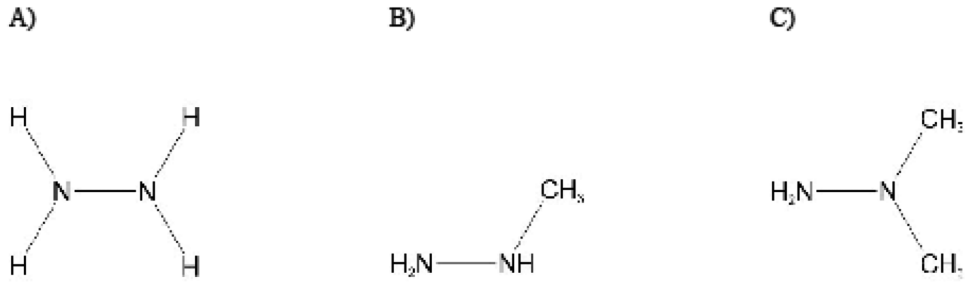

FIGURE 2. Chemical structures of (A) hydrazine and its alkyl derivatives, (B) monomethylhydrazine (MMH), and (C) 1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine, UDMH).

Hydrazine was found to be a strong convulsant at high doses, but demonstrated depressive effects at low doses.[36,37] Extreme lethargy, lack of muscle tone, and decreased ability to walk were the primary symptoms noticed in rats exposed to hydrazine. These animals would remain in a quiescent state for as long as 24 hours.[38] In animal studies, high doses of hydrazine resulted in seizures, but compared with its alkyl derivatives, seizures were not as strong and occurred at doses beyond the median lethal dose (LD_{50}).[27,38,39,40] This is also reflected in human case reports. Central nervous system depression has been most commonly described in human exposures with prolonged periods of decreased mental status or coma lasting up to 3 days.[19,21,22]

MMH and UDMH, in contrast, appear to have primarily excitatory effects on the central nervous system, with MMH being more potent than UDMH. Animal studies near-uniformly describe tonic-clonic convulsions and death by respiratory arrest after toxic doses of UDMH or MMH.[34,40,41] Compared with hydrazine, seizures in rats occurred at doses more closely associated with the LD_{50} of UDMH and MMH.[38] In humans, twitching, hyperreflexia, and clonic movements were described in two cases of individuals exposed to a 50:50 mixture of hydrazine and UDMH (Aerozine 50).[18] Agitation and convulsions were also described in a case of an individual involved in a UDMH explosion.[23] There were no human cases of acute exposure to MMH found. Generally, the alkyl derivatives are closely associated with central nervous system excitation and seizures.

Early animal studies demonstrated that acute exposure to hydrazine was associated with an elevation of gamma-amino-butyric acid (GABA) levels in the rat brain,[39] though it is unclear if this is what causes hydrazine's depressive effects. A series of animal studies by Roberts et al. in the mid-1960s hypothesized that hydrazine exerted its toxicity via interference with the urea cycle, citing an observed protective effect of arginine and ornithine against hydrazine toxicity.[40,42,43] Later metabolomics studies in rats demonstrated increased levels of argininosuccinate and Nα-acetylcitrulline supporting its hypothesized influence on the urea cycle, though it remained unclear how hydrazine exerted this effect.[44] Hydrazine is associated with increased concentration of ammonia in the cerebrospinal fluid in animal studies.[41] Although hyperammonemia was noted in a case of coma caused by inhalation hydrazine exposure, the patient had normal cerebrospinal fluid studies.[21] Hydrazine's effects on the urea cycle and its associated changes in ammonia levels in animals are hypothesized to be the possible explanation for hydrazine's neurologic effects.[1] Despite this, a clear mechanism for hydrazine toxicity on the central nervous system remains unclear.

In contrast, both UDMH and MMH are thought to exert neurologic toxicity similar in mechanism to other aliphatic and aromatic hydrazides (such as isonicotinic acid hydrazide). Both UDMH and MMH appear to affect GABA synthesis via interference of the pyridoxal-5′-phosphate (PLP) dependent glutamic acid decarboxylase (GAD).[34] This is thought to be because of formation of PLP hydrazones, which inhibit pyridoxal kinase, resulting in decreased available PLP and subsequent decreased GAD activity and reduction of GABA.[45,46] This is supported by observed decreases in GAD activity and GABA concentrations in rat brains in animals exposed to UDMH and MMH.[39] This is further supported by protective effects of pyridoxine given to animals exposed to UDMH and MMH.[41]

Hepatotoxicity

Exposure to hydrazine in animals caused hepatic damage in both chronic and acute exposures, demonstrated by changes in liver enzymes as well as on histopathological examination.[36,47,48,49] In case reports of a non-fatal inhalational exposure to hydrazine, elevation in alanine aminotransferase and aspartate aminotransferase were noted within 5 hours of exposure, lasting up to about a week, and eventual resolving after 4 to 5 weeks.[24,25] In a human case report of a fatal case of hydrazine toxicity because of chronic inhalation exposure, focal hepatic necrosis and cell degeneration were noted.[20] Similarly, individuals with chronic exposure to UDMH displayed elevated ALT as well as fatty degeneration on liver biopsy.[50] Studies in animals have noted that hydrazine may interfere with pyridoxine dependent enzymes in the liver.[42,44] Since hydrazine is a powerful reducing agent, hepatic injury could also be because of oxidative stress and depletion of reduced glutathione.[47]

Hemotoxicity

Animal and human studies have shown that hydrazine and its derivatives can cause hemolytic anemia, formation of Heinz bodies, and development of methemoglobinemia.[51] Studies have shown that MMH causes the most severe hemotoxic reactions.[52] At higher doses, hydrazine and UDMH can produce anemia, but it is less defined than MMH. It is believed that hydrazine and its derivatives will cause destruction of red cells by denaturing hemoglobin.[51] UDMH may have a separate mechanism of action for hemolytic anemia, as it does not appear to cause development of either Heinz bodies or methemoglobinemia. Previous literature in animals showed that methemoglobinemia can be detected following an acute exposure of 90 ppm MMH for less than 10 minutes.[51] Although not clearly defined, the development of methemoglobinemia suggests that oxidant stress plays a role in the anemia and hemolysis caused by MMH. Of the limited case reports involving human acute exposures, there were no reports of methemoglobin development.

Treatment

Treatment of hydrazine exposure involves decontamination, supportive measures, and pharmaceutical treatment of potential neurologic sequelae. Given few reports of acute hydrazine toxicity in humans, treatment recommendations are based largely on animal studies, observation data, and expert opinion. Patients should be quickly removed from the site of the spill to minimize exposure to fumes, a minimum of 75 feet.[53] Decontamination is critical to patient care and no patient should be transported for medical treatment until full decontamination has been completed.[33,54] All clothing should be immediately removed. Hydrazine, UDMH, and MMH are all miscible in water and can be decontaminated from the skin or eyes using copious irrigation with water for at least 15 minutes.[26,54]

On scene fire and EMS personnel in addition to aerospace or emergency medical providers should wear appropriate protective equipment, including gloves, a full protective suit, a certified vapor respirator, face shield, and rubber boots until site decontamination can be confirmed by an on-scene incident commander.[55] The source and mechanism of hydrazine exposure should be investigated immediately, as treatment decisions may be determined by exposure to specific hydrazine derivatives and any co-exposures. For example, in the F-16, if the EPU fires, as much as 24 g of unreacted hydrazine vapors are expelled in the exhaust gas.[55] However, despite this risk, approximately 99% of this hydrazine will be reacted to ammonia and water, which has separate toxicity and treatments.[11,12]

In previous reports, inhalational injuries are managed primarily with supportive measures from supplemental oxygen to endotracheal intubation for respiratory failure, if required.[19,21,23] In symptomatic patients or those with significant exposure, a chest X-ray should be obtained.[12,55] Outpatient pulmonary function testing should be included;[12] however, this likely has little practical role in the management of acute exposures.

Treatment of the neurologic sequelae of hydrazine and its alkyl derivatives has historically centered on pyridoxine to mitigate the pathologic effects on pyridoxal kinase. Although the efficacy is mixed in animal studies,[1] 25 mg/kg pyridoxine has been used in a few clinical cases.[18,19,21,23] The doses have been as a mixture of intravenous and intramuscular administration.[18,21] However, limited physiologic explanation for this dosing has been given in the literature specific to hydrazine toxicity but it falls within a reasonable margin of safety.[1] Similarly to isoniazid toxicity, repeat dosing may be required if seizures continue.[56] In animals, pyridoxine has been shown to be more effective in cases of UDMH and MMH toxicity.[38] Transfer to a large, tertiary medical center may be required, as few military facilities have intravenous pyridoxine available.[12]

Additional medications utilized to mitigate the excitatory effects of alkyl-hydrazines have included benzodiazepines and/or phenobarbital in both humans and animals.[19,23,43,57] Given the suspected differences in mechanisms of toxicity between hydrazine compared with UDMH and MMH, alternative treatment compounds have been explored including arginine and ornithine in rats. Mixtures of the two amino acids were observed to be protective against hydrazine toxicity in the animals.[41,42] Ornithine ketoglutarate had been used once in humans alongside pyridoxine in a patient exposed to UDMH, but has not otherwise been used.[23]

There are no studied treatments for the underlying liver injury associated with hydrazine exposure. However, given the proposed mechanism of toxicity, n-acetylcysteine could be considered. Soft tissue injury caused by hydrazines is managed similarly to caustic burns and, if severe, may require transfer to a burn center. Previous cases have required skin excision and grafting with favorable outcomes.[21]

Laboratory analysis during assessment of a patient with a large, acute exposure should include complete blood count, metabolic panels, liver function testing, urinalysis, and methemoglobin level. Labs should be repeated 7 days after exposure, if appropriate.[54] For military flight surgeons and physicians, after an exposure to hydrazine, the patient should not return to duty or flight status until all symptoms have resolved, including any radiographic and laboratory abnormalities. As noted by Cromar et al., the U.S. Air Force Aeromedical Consultation Service, the U.S. Army Aeromedical Activity Center, nor the U.S. Naval Aerospace Medical Institute require a waiver for return to flight once aviators once symptoms resolve and laboratory and radiologic testing has returned to baseline.[55]

Future of Hydrazine

Hydrazine fuel is used in a variety of military and aerospace applications, in part because of its unique and reliable properties. Hydrazine can be used as either a hypergolic propellant, where a fuel and oxidizer spontaneously combust when combined, or as a monopropellant, where hydrazine interacts directly with a catalytic bed. Hydrazine provides the aerospace and military industries a unique propellant. Its applications are limited, however, because of its toxicity. For decades, The U.S. Air Force, NASA, European Space Administration, and private defense contractors have funded research to develop propellants with properties similar to hydrazine, but without the toxic side effects.[6,58,59] In some circumstances, the need for hydrazine has been negated by advances in engineering. For example, the fifth-generation single-engine F-35 fighter does not rely upon a hydrazine EPU. Unlike the F-16's hydrazine powered EPU, the F-35 has a Power and Thermal Management System that relies on alternative sources of power in emergency situations.[60]

In circumstances where reliable hypergolic and monopropellant fuels are required, increasing focus has been placed in the development of Reduced Hazard Propellants or "green fuels."[6,59] The ideal propellant is one with low toxicity and low volume, provides reliable energy, is easy to store, and is low cost. In June 2019, NASA launched the Green Propellant Infusion Mission to test hydroxylammonium nitrate (NH_3OHNO_3), also known as "AF-M315E, and a proposed alternative to monopropellant hydrazine."[61] This fuel was developed by the Air Force Research Lab and can be safely handled in open containers without need of respiratory protective equipment.[62] It is hoped that these Reduced Hazard Propellants may provide ideal alternatives to hydrazine, negating the need for military and aerospace use of the toxic propellant.

CONCLUSION

Hydrazine, MMH, and UDMH are three highly toxic propellants used commonly in the military and aerospace industries. Although there are limited reports of human toxicity, there is evidence that hydrazine and its derivatives can cause severe neurologic, pulmonary, hepatic, hematologic, and soft tissue injury. Treatment relies mainly upon supportive care. High-dose pyridoxine may be required for treatment of neurologic sequelae. Research is ongoing to replace hydrazine with less-toxic alternatives, negating the need for continued use of the highly toxic propellant.

ACKNOWLEDGMENTS

The authors confirm contribution to the article as follows: C.D.N., study concept and design; H.N.N. and C.D.N., acquisition of the data; H.N.N. and C.D.N., analysis of the data; H.N.N. and C.D.N., drafting of the manuscript; H.N.N., J.A.C., V.S.B., T.E.A., and C.D.N., critical revision of the manuscript; and H.N.N., J.A.C., V.S.B., T.E.A., and C.D.N., approval of final manuscript.

FUNDING

None declared.

CONFLICT OF INTEREST STATEMENT

There are no conflicts on interest for any author.

REFERENCES

1. Zelnick SD, Mattie DR, Stepaniak PC: Occupational exposure to hydrazines: treatment of acute central nervous system toxicity. Aviat Space Environ Med 2003; 74(12): 1285-91.
2. Troyan JE: Properties, production, and uses of hydrazine. Ind Eng Chem 1953; 45(12): 2608-12.
3. Simpson DK: Safety and handling of hydrazine. Olin Corp. Olin Corporation Research Center. 1986. https://apps.dtic.mil/sti/citations/ADP005339.
4. Suarez-Alfonso E, Chambers AE, Hatz DJ: Hydrazine handling manual. Rocketdyne Canoga Park; 1961. https://apps.dtic.mil/seo/citations/AD0266145.
5. Garcia HD, James JT, Limero TF: Human exposure limits to hypergolic fuels. Houston, TX, NASA Johnson Space Center. 1992. https://ntrs.nasa.gov/search.jsp?R=19920013112.
6. Hasan D, Grinstein D, Kuznetsov A, et al.: Green comparable alternatives of hydrazines-based monopropellant and bipropellant rocket systems. Aerosp Eng February 2019;
7. Makarovsky I, Markel G, Dushnitsky T, Eisenkraft A: Hydrazine—the space era agent. Isr Med Assoc J 2008; 10(4): 302-6.
8. Lombardi AR, Lurie AS: Health hazards encountered in repair of jet aircraft fuel cells. J Am Med Assoc 1957; 164(5): 531-3.
9. Environment Canada, Health Canada. Hydrazine. January 2011. https://www.ec.gc.ca/ese-ees/17647095-B851-46F4-A4BB-79F887D84666/batch10_302-01-2_en.pdf.
10. Back KC, Carter VL, Thomas AA: Occupational hazards of missile operations with special regard to the hydrazine propellants. Aviat Space Environ Med 1978; 49(4): 591-8.
11. Suggs H, Luskus L, Kilian H, Mokry J: Exhaust gas composition of the F-16 Emergency Power Unit. No. SAM-TR-79-2. United States Air Force School of Aerospace Medicine, Brooks Air Force Base, 1979.
12. Brough MB: Best Practices: Emergency Medical Management to Hydrazine Exposure. Dayton OH, Wright State University, 2016.
13. Aerojet Rocketdyne: Monopropellant rocket engines. https://www.rocket.com/space/space-power-propulsion/monopropellant-rocket-engines.
14. Federal Aviation Administration: Draft environmental assessment for issuing SpaceX a launch license for an in-flight dragon abort test. Kennedy Space Center, Brevard County, Florida. November 2018. https://www.faa.gov/about/office_org/headquarters_offices/ast/environmental/nepa_docs/review/launch/media/Draft_EA_for_SpaceX_In-flight_Dragon_Abort_508.pdf.
15. Christensen WD: Industrial hygiene and the F-16 air combat fighter. Aviat Space Environ Med 1981; 52(3): 147-9.
16. McLendon MH: Development of occupational and environmental health criteria for the F-16. Aviat Space Environ Med 1981; 52(3): 145-7.
17. Moher D, Shamseer L, Clarke M, et al: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4(1): 1.
18. Frierson WB: Use of pyridoxine HCL in acute hydrazine and UDMH intoxication. Ind Med Surg 1965; 34: 650-1.
19. Reid FJ: Hydrazine poisoning. Br Med J 1965; 2(5472): 1246.
20. Sotaniemi E, Hirvonen J, Isomäki H, Takkunen J, Kaila J: Hydrazine toxicity in the human. report of a fatal case. Ann Clin Res 1971; 3(1): 30-3.
21. Kirklin JK, Watson M, Bondoc CC, Burke JF: Treatment of hydrazine-induced coma with pyridoxine. N Engl J Med 1976; 294(17): 938-9.
22. Harati Y, Niakan E: Hydrazine toxicity, pyridoxine therapy, and peripheral neuropathy. Ann Intern Med 1986; 104(5): 728-9.

23. Dhennin C, Vesin L, Feauveaux J: Burns and the toxic effects of a derivative of hydrazine. Burns Incl Therm Inj 1988; 14(2): 130-4.
24. Kao YH, Chong CH, Ng WT, Lim D: Hydrazine inhalation hepatotoxicity. Occup Med (Lond) 2007; 57(7): 535-7.
25. Binyamin Y, Frenkel A, Brotfain E, et al: Elevated CPK levels after hydrazine inhalation exposure in an F16 aircraft technician. Toxicology Reports 2018; 5: 927-8.
26. The National Institute for Occupational Safety and Health (NIOSH): Hydrazine. October 2019.
27. Comstock CC, Lawson LH, Greene EA, Oberst FW: Inhalation toxicity of hydrazine vapor. AMA Arch Ind Health 1954; 10(6): 476-90.
28. Jacobson KH, Clem JH, Wheelwright HJ, Rinehart WE, Mayes N: The acute toxicity of the vapors of some methylated hydrazine derivatives. AMA Arch Ind Health 1955; 12(6): 609-16.
29. Cross JB: Hydrazine monitoring in spacecraft. NASA Johnson Space Center; Houston, TX. 1992. https://ntrs.nasa.gov/search.jsp?R=19920013113.
30. Smith EB, Clark DA: Absorption of hydrazine through canine skin. Toxicol Appl Pharmacol 1972; 21(2): 186-93.
31. Evans DM: Two cases of hydrazine hydrate dermatitis without systemic intoxication. Occup Environ Med 1959; 16(2): 126-7.
32. Wrangsjö K, Mårtensson A: Hydrazine contact dermatitis from gold plating. Contact Derm 1986; 15(4): 244-5.
33. James JTP: Aerospace toxicology and microbiology. NASA Johnson Space Center; Houston, TX. 2007. https://ntrs.nasa.gov/search.jsp?R=20070032022.
34. Back KC, Thomas AA: Pharmacology and Toxicology of 1,1-Dimethyl-Hydrazine (UDMG). United States Air Force Aerospace Medical Research Lab, Wright Patterson Air Force Base, OH; 1962. https://apps.dtic.mil/seo/citations/AD0292689.
35. Keller WC: Toxicity assessment of hydrazine fuels. Aviat Space Environ Med 1988; 59(11 Pt 2): A100-106.
36. MacEwen JD: The effects of 6-month chronic low level inhalation exposures to hydrazine on animals. United States Air Force Aerospace Medical Research Lab. Wright Patterson Air Force Base, OH; 1974. https://apps.dtic.mil/seo/citations/ADA011865.
37. Back KC, Thomas AA: Aerospace problems in pharmacology and toxicology. Annu Rev Pharmacol 1970; 10: 395-412.
38. O'Brien RD, Kirkpatrick M, Miller PS: Poisoning of the rat by hydrazine and alkylhdrazines. Toxicol Appl Pharmacol 1964; 6(4): 371-7.
39. Medina MA: The in vivo effects of hydrazines and vitamin B6 on the metabolism of gamma-aminobutyric acid. J Pharmacol Exp Ther 1963; 140: 133-7.
40. Roberts E, Simonsen DG, Roberts E: Arginine protection against hydrazine toxicity. Biochem Pharmacol 1963; 12(12): 1445-7.
41. Weir FW, Nemenzo JH, Bennett S, Meyers FH: A Study of the Mechanism of Acute Toxic Effects of Hydrazine. UDMH, MMH, and SDMH. Techn Doc No AMRL-TDR-64-26. San Francisco, CA, Hine Labs, 1964, 1-27.
42. Roberts E, Simonsen DG, Roberts E: Structural requirements of nitrogenous substances which have protective effects against acute hydrazine toxicity in mice. Proc Soc Exp Biol Med 1965; 119(3): 683-7.
43. Roberts E, Simonsen DG: Biochemical studies on acute hydrazine toxicity in mice. City of Hope Medical Center. 1966: 1-15.
44. Nicholls AW, Holmes E, Lindon JC, et al: Metabonomic investigations into hydrazine toxicity in the rat. Chem Res Toxicol 2001; 14(8): 975-87.
45. Tapia R, Awapara J: Effects of various substituted hydrazones and hydrazines of pyridoxal-5′-phosphate on brain glutamate decarboxylase. Biochem Pharmacol 1969; 18(1): 145-52.
46. Wiegand RG: The formation of pyridoxal and pyridoxal 5-phosphate hydrazones1. J Am Chem Soc 1956; 78(20): 5370-5309.
47. Hussain SM, Frazier JM: Cellular toxicity of hydrazine in primary rat hepatocytes. Toxicol Sci 2002; 69(2): 424-32.
48. Patrick RL, Back KC: Pathology and toxicology of repeated doses of hydrazine and 1,1-dimethylhydrazine in monkeys and rats. AMRL-TDR-64-43. Aerospace Medical Research Laboratories. 1964: 1-14.
49. Keop S: Toxicology of hydrazine. A Review Arch Indust Hyg & Occupational Med 1954; 9(3): 199-204.
50. Petersen P, Bredahl E, Lauritsen O, et al: Examination of the liver in personnel working with liquid rocket propellant. Occup Environ Med 1970; 27(2): 141-6.
51. George M, Johnson W, Back K: Effects of propellant hydrazines on red blood cells: methemoglobin and Heinz body formation. United States Air Force Aerospace Medical Research Lab, Wright Patterson Air Force Base, OH; 1978. https://apps.dtic.mil/sti/pdfs/ADA064133.pdf.
52. Clark DA, Bairrington JD, Bitter HL, et al: Pharmacology and toxicology of propellant hydrazines. Aeromed Rev 1968; 11: 1-126.
53. Hydrazine Response Procedures, Edwards Air Force Base Instruction: 21-9. November 2004.
54. United States Air Force. Emergency Management of Personnel Exposure to Hydrazine, Vance Air Force Base Instruction: 48-105. November 2011.
55. Cromar JW: You're the flight surgeon: hydrazine exposure. Aviat Space Environ Med 2013; 84(5): 540-1.
56. MERCK Index: Hydrazine (CAS RN: 302-01-2). https://webwiser.nlm.nih.gov/substance?substanceId=224&identifier=Hydrazine&identifierType=name&menuItemId=1&catId=162.
57. Brophy GM, Bell R, Claassen J, et al: Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012; 17(1): 3-23.
58. Hawkins T: Green Propulsion - A USAF Overview. United States Air Force Research Lab, Edwards Air Force Base, California; 2002. https://apps.dtic.mil/seo/citations/ADA405749.
59. Sackheim RL, Masse RK: Green propulsion advancement: challenging the maturity of monopropellant hydrazine. J Propul and Power 2014; 30(2): 265-76.
60. Wiegand C: F-35 Air Vehicle Technology Overview. In: 2018 Aviation Technology, Integration, and Operations Conference. Atlanta, Georgia: American Institute of Aeronautics and Astronautics; 2018.
61. National Aeronautics and Space Administration: Green Propellant Infusion Mission (GPIM) overview. Houston, TX, NASA Johnson Space Center. 1992. https://www.nasa.gov/mission_pages/tdm/green/overview.html.
62. Masse R, Allen M, Spores R, Driscoll EA: AF-M315E Propulsion System Advances and Improvements. Salt Lake City, UT: American Institute of Aeronautics and Astronautics; 2016.